

# UK Patent Application (19) GB (11) 2 276 162 (13) A

(43) Date of A Publication 21.09.1994

(21) Application No 9305469.0

(22) Date of Filing 17.03.1993

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(51) INT CL<sup>5</sup>

C07D 211/26 211/34 401/12

(52) UK CL (Edition M )

C2C CAA CKK CKP CKR CKZ CLG CSF C1530 C1532  
C215 C22Y C220 C226 C246 C25Y C250 C251 C271  
C28X C280 C281 C29X C29Y C30Y C32Y C322 C34Y  
C342 C350 C351 C355 C36Y C360 C362 C364 C365  
C366 C367 C385 C45Y C455 C51X C510 C536 C57Y  
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C633 C652 C659 C660 C662 C668 C680 C682 C699  
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U1S S2417

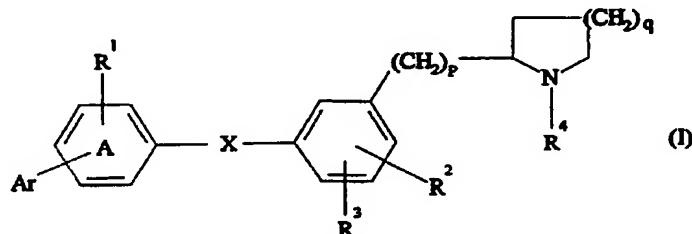
(56) Documents Cited  
None

(58) Field of Search

UK CL (Edition M ) C2C  
INT CL<sup>5</sup> C07D  
Online database CAS Online

## (54) Aniline and benazilide derivatives

## (57) Compounds of the general formula (I):-



or a physiologically acceptable salt or solvate thereof, in which

R<sup>1</sup> represents a hydrogen atom or a halogen atom or a C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy group;

R<sup>2</sup> and R<sup>3</sup> which may be the same or different, each independently represent a hydrogen atom or a halogen atom, or a hydroxy, C<sub>1-6</sub>alkoxy or C<sub>1-6</sub>alkyl group;

R<sup>4</sup> represents a hydrogen atom or a C<sub>1-6</sub>alkyl group;

Ar represents an optionally substituted phenyl or pyridyl group,

X represents -CONH-, -NHCO-, -CH<sub>2</sub>NH- or -NHCH<sub>2</sub>-;

p represents an integer from 1 to 3; and

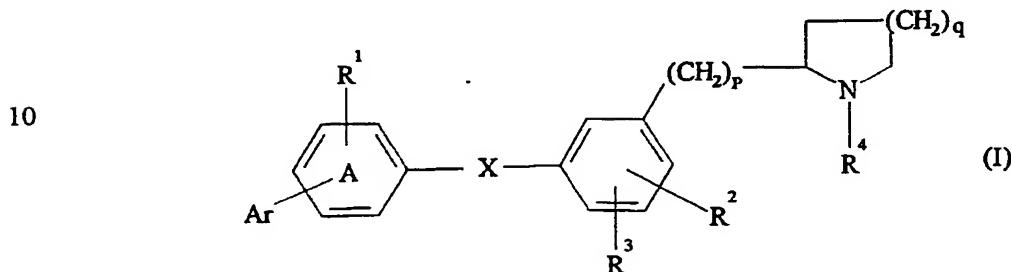
q represents an integer from 1 to 3; are 5-HT<sub>1D</sub> antagonists useful in the treatment of CNS disorders, endocrine disorders and sexual dysfunction.

GB 2 276 162 A

CHEMICAL COMPOUNDS

This invention relates to novel aniline and benzanimide derivatives, to processes for their preparation, and to pharmaceutical compositions containing them.

5 According to the present invention there is provided compounds of the general formula (I) :-



or a physiologically acceptable salt or solvate thereof, in which

15  $R^1$  represents a hydrogen atom or a halogen atom or a  $C_{1-6}$ alkyl or  $C_{1-6}$ alkoxy group;  
 $R^2$  and  $R^3$  which may be the same or different, each independently represent a hydrogen atom or a halogen atom, or a hydroxy,  $C_{1-6}$ alkoxy or  $C_{1-6}$ alkyl group;  
 $R^4$  represents a hydrogen atom or a  $C_{1-6}$ alkyl group;

20 Ar represents a phenyl group optionally substituted by one or two substituents selected from halogen atoms, or  $C_{1-6}$ alkyl, hydroxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, hydroxy,  $-CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^5$ ,  $-COR^6$ ,  $-SR^6$ ,  $-SOR^6$ ,  $-SO_2R^6$ ,  $-CR^6=NOR^7$ ,  $-CONR^6R^7$ ,  $-CONR^6SO_2R^7$ ,  $-CONR^6(CH_2)_mCO_2R^7$ ,  $-CONR^6(CH_2)_mOC_{1-4}$ alkyl,  $-SO_2NR^6R^7$ ,  $-OC(O)NR^6R^7$ ,  $-(CH_2)_nNR^8R^9$ ,  $-(CH_2)_nOC(O)C_{1-4}$ alkyl (optionally substituted by a  $C_{1-6}$ alkoxy group), or  $C_{1-4}$ alkoxyalkyl (optionally substituted by a  $C_{1-4}$ alkoxy or hydroxy group), a 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,5-oxadiazol-3-yl, imidazol-1-ylmethyl, dioxolan or thioxolan group (each of which may be optionally substituted by a  $C_{1-3}$ alkyl group) or, when two substituents are attached to adjacent carbon atoms, they may form a 5- or 6-membered saturated fused ring which contains one or two oxygen atoms and which may be optionally substituted by an oxo group;

25

or Ar represents a pyridinyl group optionally substituted by one or two substituents selected from halogen atoms, C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, hydroxy, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sup>6</sup>, -COR<sup>6</sup>, -CONR<sup>6</sup>R<sup>7</sup> and -(CH<sub>2</sub>)<sub>m</sub>OC(O)C<sub>1-4</sub>alkyl;

R<sup>5</sup> represents a hydrogen atom or a C<sub>1-6</sub>alkyl group optionally substituted by one or two substituents selected from C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, hydroxy or -NR<sup>6</sup>R<sup>7</sup>;

R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> which may be the same or different, each independently represent a hydrogen atom or a C<sub>1-6</sub>alkyl group;

or -NR<sup>6</sup>R<sup>7</sup> forms a saturated heterocyclic ring which has 5 or 6 ring members which, when there are 6 ring members, may optionally contain in the ring one oxygen or sulphur atom;

R<sup>9</sup> represents a hydrogen atom or a C<sub>1-6</sub>alkyl, -COR<sup>10</sup> or -SO<sub>2</sub>R<sup>11</sup> group;

or -NR<sup>8</sup>R<sup>9</sup> forms a saturated heterocyclic ring which has 5 or 6 ring members, may optionally be substituted by an oxo group and, when there are 6 ring members, may optionally contain in the ring one oxygen or sulphur atom;

R<sup>10</sup> represents a hydrogen atom or a group selected from C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy or a C<sub>1-4</sub>alkoxyalkyl group;

R<sup>11</sup> represents a C<sub>1-6</sub>alkyl or phenyl group;

X represents -CONH-, -NHCO-, -CH<sub>2</sub>NH- or -NHCH<sub>2</sub>-;

m represents an integer from 1 to 3;

n represents zero or an integer from 1 to 3;

20 p represents an integer from 1 to 3; and

q represents an integer from 1 to 3.

It is to be understood that the present invention encompasses all geometric and optical isomers of the compounds of general formula (I) and their mixtures including the racemic mixtures thereof.

25 Physiologically acceptable salts of the compounds of formula (I) include acid addition salts formed with inorganic or organic acids (for example hydrochlorides, hydrobromides, sulphates, phosphates, benzoates, naphthoates, hydroxynaphthoates, p-toluenesulphonates, methanesulphonates, sulphamates, ascorbates, tartrates, citrates, oxalates, maleates, salicylates, fumarates, succinates, lactates, glutarates, glutaconates,

acetates or tricarballylates) and, where appropriate, inorganic base salts such as alkali metal salts (for example sodium salts).

In the compounds of formula (I), the term " $C_{1-6}$ alkyl" or " $C_{1-6}$ alkoxy" as a group or part of a group means that the group is straight or branched and consists of 1 to 6 carbon atoms. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy. The term "halogen" means fluorine, chlorine, bromine or iodine.

Within the above definition, when Ar represents a phenyl group substituted by two substituents which are attached to adjacent carbon atoms and together form a 5- or 6-membered saturated fused ring which contains one or two oxygen atoms and which may be optionally substituted by an oxo group, suitable groups include  $-C(O)OCH_2-$ ,  $-OCH_2O-$  or  $-CH_2OCH_2O-$ .

Within the above definition, when  $-NR^6R^7$  or  $-NR^8R^9$  represent a saturated heterocyclic ring, these contain 5 or 6 ring members, one of which (when there are 6 ring members) may be an oxygen or a sulphur atom. Suitable heterocyclic groups are a pyrrolidinyl, piperidinyl, morpholinyl or thiomorpholinyl group.

Where a saturated heterocyclic ring is formed by the group  $-NR^8R^9$  and said ring is substituted by an oxo group, suitable heterocyclic groups include a 2-oxo-1-pyrrolidinyl, 4-oxo-3-thiazolidinyl or 2-oxo-tetrahydro-1,3-thiazinyl group.

Ar may preferably be attached in the meta or more particularly the para position of the phenyl ring A relative to the group X.

When Ar is substituted by a single atom or group as defined above the substituent is preferably attached in a position meta or para to the phenyl ring A in general formula (I). When Ar is substituted by two atoms or groups as defined above one substituent is preferably attached in the position para to, and the other is in a position ortho to the phenyl ring A in general formula (I).

A preferred group of compounds of general formula (I) is that wherein Ar is substituted by one or two substituents as defined in general formula (I) wherein one

substituent is in the position para to the phenyl ring A in general formula (I) the second substituent is in the position ortho to the phenyl ring A in general formula (I).

Another preferred group of compounds of general formula (I) is that wherein Ar is substituted by a single substituent as defined in general formula (I) wherein said substituent is in the position para to the phenyl ring A in general formula (I).

A further preferred group of compounds of general formula (I) is that wherein Ar is a phenyl group optionally substituted by a C<sub>1-6</sub>alkyl, especially methyl, group; a hydroxyC<sub>1-6</sub>alkyl, especially 1-hydroxyethyl, group; hydroxy; -CO<sub>2</sub>R<sup>5</sup> where R<sup>5</sup> is a hydrogen atom or a C<sub>1-6</sub>alkyl, especially methyl, or ethyl, group; -COR<sup>6</sup> where R<sup>6</sup> is a hydrogen atom or a C<sub>1-6</sub>alkyl, especially methyl, group; -CONR<sup>6</sup>R<sup>7</sup> where R<sup>6</sup> and R<sup>7</sup> each independently represent a hydrogen atom or a C<sub>1-6</sub>alkyl, especially methyl, group; or -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup> where R<sup>6</sup> and R<sup>7</sup> each independently represent a hydrogen atom or a C<sub>1-6</sub>alkyl, especially methyl, group.

Another preferred group of compounds of general formula (I) is that wherein Ar represents a phenyl group substituted by a group selected from 1-hydroxyethyl, hydroxy, -CO<sub>2</sub>H, -CHO, -COCH<sub>3</sub>, -CONH<sub>2</sub> or -SO<sub>2</sub>NH<sub>2</sub>, and optionally further substituted by a methyl group.

A further preferred group of compounds of general formula (I) is that wherein Ar is a 3-pyridinyl, or more preferably a 4-pyridinyl, group.

Where Ar represents a pyridinyl group substituted by a single substituent, particularly preferred are those compounds wherein the substituent on the pyridinyl group is in a position ortho to the bond to the phenyl ring A in general formula (I).

Also preferred is the group of compounds of general formula (I) wherein R<sup>1</sup> is a hydrogen atom or a C<sub>1-6</sub>alkyl, especially methyl, group.

Another preferred group of compounds of general formula (I) is that wherein R<sup>1</sup> is attached at a position ortho to Ar on the phenyl ring A in general formula (I).

Another preferred group of compounds of general formula (I) is that wherein R<sup>2</sup> is attached in the para-position relative to the group X.

A further preferred group of compounds of general formula (I) is that wherein R<sup>2</sup> is a halogen atom, especially a fluorine or chlorine atom, or a hydroxy or C<sub>1-6</sub>alkoxy, especially methoxy, group.

Also preferred is the group of compounds of general formula (I) wherein R<sup>3</sup> is a 5 hydrogen atom or a fluorine atom.

A yet further preferred group of compounds of general formula (I) is that wherein R<sup>4</sup> represents a C<sub>1-6</sub>alkyl, especially methyl, group.

Another preferred group of compounds of general formula (I) is that wherein X represents -NHCO- or -CONH-.

10 Another preferred group of compounds of general formula (I) is that wherein p is 2.

A further preferred group of compounds is that wherein q is 2.

Preferred compounds of general formula (I) include:

N-[[4'-aminocarbonyl][1,1'-biphenyl]-4-yl]-3-[2-(1-methyl-2-piperidinyl)ethyl]-4-methoxybenzamide;

15 N-[4'-(1-hydroxyethyl)][1,1'-biphenyl]-4-yl]-4-methoxy-3-[2-(1-methyl-2-piperidinyl)ethyl]benzamide;

N-(4'-acetyl[1,1'-biphenyl]-4-yl)-4-methoxy-3-[2-(1-methyl-2-piperidinyl)ethyl]benzamide;

and their physiologically acceptable salts and solvates.

20 Particularly preferred compounds of general formula (I) include:

N-(4'-acetyl[1,1'-biphenyl]-4-yl)-4-hydroxy-3-[2-(1-methyl-2-piperidinyl)ethyl]benzamide;

4-hydroxy-N-(4'-hydroxy[1,1'-biphenyl]-4-yl)-3-[2-(1-methyl-2-piperidinyl)ethyl]benzamide;

25 N-(4'-formyl-2'-methyl[1,1'-biphenyl]-4-yl)-4-methoxy-3-[2-(1-methyl-2-piperidinyl)ethyl]benzamide;

and their physiologically acceptable salts and solvates.

5-Hydroxytryptamine (serotonin) is a neurotransmitter which is widely distributed within the central nervous system (CNS), platelets and the gastrointestinal tract. Changes in transmission in serotonergic pathways in the CNS are known to modify, for example,

mood, psychomotor activity, appetite, memory and blood pressure. Release of 5-hydroxytryptamine from platelets can mediate vasospasm while changes in free 5-hydroxytryptamine levels in the gastrointestinal tract can modify secretion and motility.

Abundant pharmacological studies have led to the discovery of multiple types of receptors for 5-hydroxytryptamine, thus providing a molecular basis to the diversity of its actions. These receptors are classed as 5-HT<sub>1</sub>, 5-HT<sub>2</sub> and 5-HT<sub>3</sub>, with 5-HT<sub>1</sub> receptors being sub-classified as 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>1C</sub>, 5-HT<sub>1D</sub> and 5-HT<sub>1D</sub>(like) receptors. The identification of these classes and sub-classes of receptor is based mainly on radioligand binding studies.

Compounds having a selective antagonist action at 5-HT<sub>1D</sub> receptors such as those described herein may exhibit a beneficial effect on subjects suffering from CNS disorders.

In the present specification, a 5-HT<sub>1D</sub> antagonist is a non-naturally occurring (synthetic) compound that specifically and selectively antagonises 5-HT<sub>1D</sub> receptors, i.e. blocks the specific actions of 5-hydroxytryptamine mediated by 5-HT<sub>1D</sub> receptors. Such compounds may be identified by a high level of affinity (pKi  $\geq$  8) in the *in vitro* human cortex and guinea-pig striatum radioligand binding assays described by Hoyer *et al*, *Neuroscience Letters*, 1988, 85, p357-362. Activity at 5-HT<sub>1D</sub> receptors may be confirmed *in vivo* using the guinea pig rotation model described by G A Higgins *et al*, *Br. J. Pharmacol.*, 1991, 102, p305-310.

The affinity of a compound for 5-HT<sub>1A</sub>, 5-HT<sub>1C</sub> and/or 5-HT<sub>2</sub> receptors is measured using the *in vitro* tests described in the following publications:

5-HT <sub>1A</sub>	Gozlan <i>et al</i> , <i>Nature</i> , 1983, <u>305</u> , p140-142
5-HT <sub>1C</sub>	Pazos <i>et al</i> , <i>Eur. J.Pharmacol.</i> , 1984, <u>106</u> , p531-538
5-HT <sub>2</sub>	Humphrey <i>et al</i> , <i>Br. J. Pharmacol.</i> , 1988, <u>94</u> , p1123-1132 (rabbit aorta model).

Thus, for example, compounds of the present invention have been shown to inhibit 5-hydroxytryptamine induced contraction of the dog isolated saphenous vein and to

antagonise the 5-hydroxytryptamine induced inhibition of neurotransmission in central and peripheral neurones.

5  $5\text{-HT}_{1D}$  antagonists, and in particular the compounds of the present invention, may therefore be of use in the treatment of CNS disorders such as mood disorders, including depression, seasonal affective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnestic disorders and age-associated memory impairment; and disorders of eating behaviour, including anorexia nervosa and bulimia nervosa. Other CNS disorders include 10 Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

15  $5\text{-HT}_{1D}$  antagonists, and in particular compounds of the present invention, may also be of use in the treatment of endocrine disorders such as hyperprolactinaemia, the treatment of vasospasm (particularly in the cerebral vasculature) and hypertension, as well as disorders in the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction.

20 Therefore, according to a second aspect of the invention, we provide a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy.

25 According to a further aspect of the present invention, we therefore provide a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

According to another aspect of the invention, we provide the use of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a therapeutic agent for the treatment of the aforementioned disorders.

30 According to a further aspect of the invention, we provide, a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof.

In particular, according to another aspect of the present invention, we provide a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

It will be appreciated that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents such as tricyclic antidepressants (e.g. amitriptyline, dothiepin, doxepin, trimipramine, butriptyline, clomipramine, desipramine, imipramine, iprindole, lofepramine, nortriptyline or protriptyline), monoamine oxidase inhibitors (e.g. isocarboxazid, phenelzine or tranylcyclopramine) or 5-HT reuptake inhibitors (e.g. fluvoxamine, sertraline, fluoxetine or paroxetine), and/or antiparkinsonian agents such as dopaminergic antiparkinsonian agents (e.g. levodopa, preferably in combination with a peripheral decarboxylase inhibitor e.g. benserazide or carbidopa), or a dopamine agonist e.g. bromocriptine, lysuride or pergolide). It is to be understood that the present invention covers the use of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof in combination with one or more other therapeutic agents.

Thus there is provided in a further or alternative aspect of the present invention a compound of general formula (I) or a physiologically acceptable salt or solvate thereof and an antidepressant agent in the presence of each other in the human or non-human animal body for use in the treatment of the aforementioned disorders.

While it is possible that a compound of general formula (I) may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The compounds of general formula (I) and their physiologically acceptable salts and solvates may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions comprising at least one compound of general formula (I) or a physiologically acceptable salt or solvate thereof. Such compositions may be presented for use in a conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Thus, the compositions according to the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation. Oral administration is preferred.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methylcellulose, glucose/sugar syrup, gelatin, hydroxypropyl methylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or

emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

5 For administration by inhalation either orally or nasally the compositions according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be 10 determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation the compositions according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges 15 of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

The pharmaceutical formulations according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

20 The compositions according to the invention may be prepared by mixing the various ingredients using conventional means.

It will be appreciated that the amount of a compound of general formula (I) required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician 25 or veterinarian. In general, however, a proposed dose of the compounds of the invention for administration in man is 0.5 to 1000mg, preferably 1 to 200mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

30 The compounds of the invention may be prepared by a number of processes as described in the following. In describing the processes which may be used for preparing the compounds of general formula (I) or intermediates useful in the preparation thereof,

any of  $R^1$ - $R^{11}$ , m and n in the various formulae are as defined in general formula (I) unless otherwise stated.

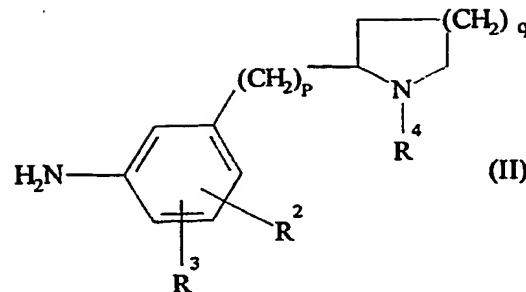
It will be appreciated that in the following methods for the preparation of compounds of general formula (I), for certain reaction steps it may be necessary to protect various reactive substituents in the starting materials for a particular reaction and subsequently to remove the protecting group. Such protection and subsequent deprotection may be particularly pertinent where  $R^4$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and/or  $R^9$  in intermediates used to prepare compounds of general formula (I) are hydrogen atoms. Standard protection and deprotection procedures can be employed, for example formation of a phthalimide (in the case of a primary amine), benzyl, trityl, benzyloxycarbonyl or trichloroethoxycarbonyl derivatives. Subsequent removal of the protecting group is achieved by conventional procedures. Thus a phthalimide group may be removed by treatment with hydrazine or a primary amine, for example methylamine. Benzyl or benzyloxycarbonyl groups may be removed by hydrogenolysis in the presence of a catalyst e.g. palladium, and trichloroethoxycarbonyl derivatives may be removed by treatment with zinc dust. Trityl groups may be removed under acidic conditions using standard procedures.

It may also be necessary in some cases to protect carboxylic acid groups (e.g. as esters) or aldehyde or ketone groups (e.g. as acyclic or cyclic acetals or ketals or as thioacetals or thioketals). Subsequent removal of these protecting groups is achieved by conventional procedures. Thus for example alkyl esters may be removed under conditions of acidic or basic hydrolysis, benzyl esters may be removed by hydrogenolysis in the presence of a catalyst e.g. palladium. Acyclic or cyclic acetals or ketals may be removed under conditions of acidic hydrolysis and thioacetals and thioketals may be removed using a mercuric salt.

Hydroxyl groups may also need protection and these may be adequately protected under amenable conditions as their esters or trialkylsilyl, tetrahydropyran and benzyl ethers. Such derivatives may be deprotected by standard procedures.

According to one general process (1A), the compounds of general formula (I) in which X represents the group -CONH-, may be prepared by a carbonylation reaction involving an aniline (II)

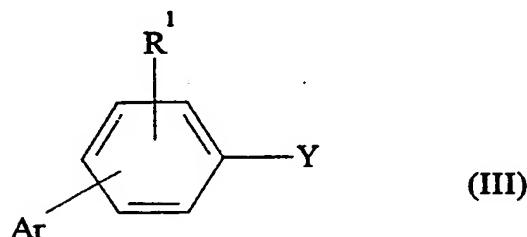
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(II)

(where  $R^2$ ,  $R^3$ ,  $R^4$ ,  $p$  and  $q$  are as defined in general formula (I)) and a halophenyl compound (III)

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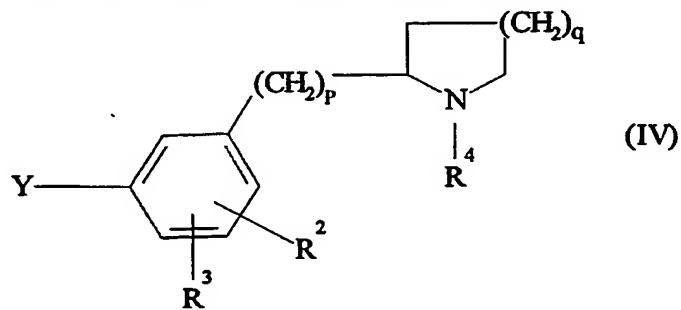
(III)

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(where  $R^1$  and  $Ar$  are as defined in general formula (I) and  $Y$  is a bromine or iodine atom or the group  $-OSO_2CF_3$ ).

Alternatively, according to the general process (1B), the compounds of general formula (I), in which  $X$  represents the group  $-NHCO-$ , may be prepared by a carbonylation reaction involving a halophenyl compound (IV)

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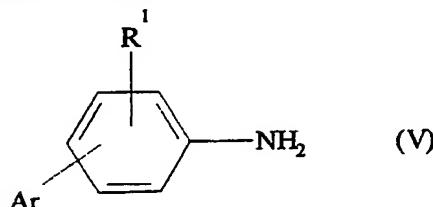
(IV)

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(where  $R^2$ ,  $R^3$ ,  $R^4$ ,  $p$  and  $q$  are as defined in general formula (I) and  $Y$  represents a

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bromine or iodine atom or the group  $-\text{OSO}_2\text{CF}_3$ ) and an aniline of formula (V)

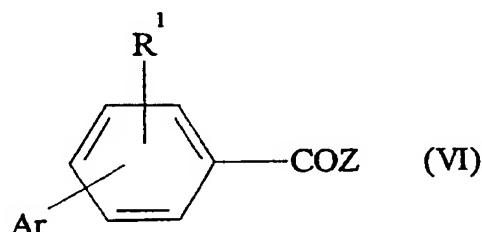


(where  $\text{R}^1$  and  $\text{Ar}$  are as defined in general formula (I)).

Both reactions take place, for example, in the presence of carbon monoxide using a palladium salt as a catalyst. The reaction is effected in the presence of a suitable base e.g. a trialkylamine such as triethylamine or tri-n-butylamine and may be conducted in a suitable solvent such as an amide e.g. dimethylformamide or a nitrile e.g. acetonitrile at a temperature within the range of  $-10^\circ\text{C}$  to  $+150^\circ\text{C}$ .

Suitable palladium salts for the reaction include triarylphosphine palladium (II) salts such as bis(triphenylphosphine)palladium (II) chloride.

15 According to another general process (2A), the compounds of general formula (I), in which  $\text{X}$  represents the group  $-\text{CONH}-$ , may be prepared by reacting an aniline of formula (II) with an activated carboxylic acid derivative of formula (VI)

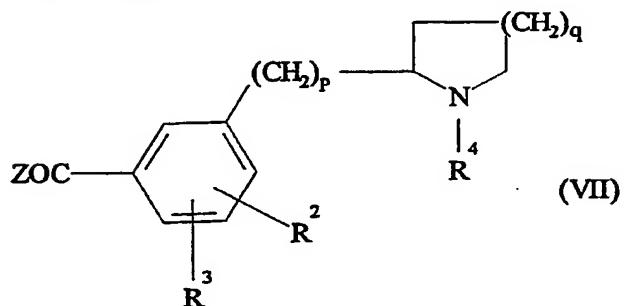


(where  $\text{Z}$  is a leaving group).

25 Alternatively, according to the general process (2B), the compounds of general formula (I), in which  $\text{X}$  represents the group  $-\text{NHCO}-$ , may be prepared by reacting an

aniline of formula (V) with an activated carboxylic acid derivative of formula (VII)

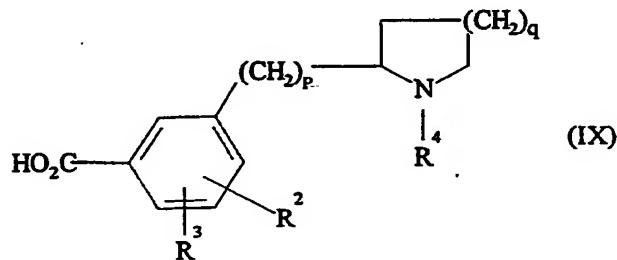
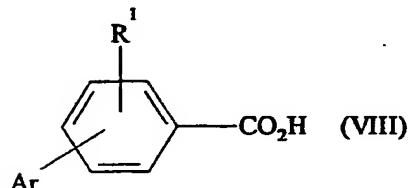
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(where Z is a leaving group).

10 Suitable activated carboxylic acid derivatives represented in formulae (VI) and (VII) include acyl halides (e.g. acid chlorides) and acid anhydrides including mixed anhydrides. These activated derivatives may be formed from the corresponding acids of formulae (VIII) or (IX)

15



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respectively, by well known procedures. For example, acid chlorides may be prepared by reaction with phosphorus pentachloride, thionyl chloride or oxalyl chloride and acid anhydrides may be prepared by reaction with an appropriate acid anhydride (e.g. trifluoroacetic anhydride), an acid chloride (e.g. acetyl chloride), an alkyl or aralkyl haloformate (e.g. ethyl or benzyl chloroformate) or methanesulphonyl chloride.

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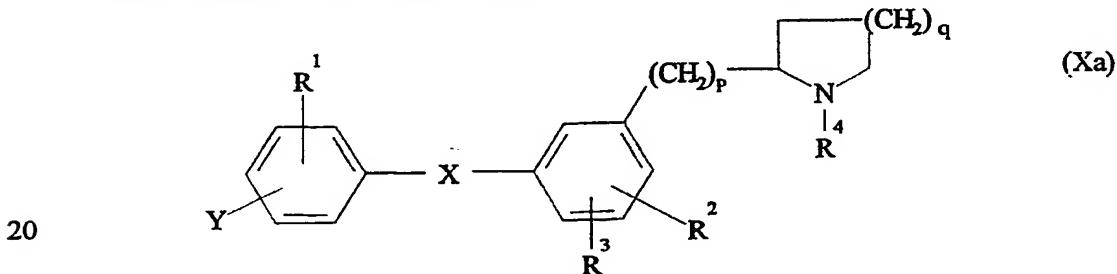
Activated carboxylic acid derivatives of formulae (VI) and (VII) may also be prepared *in situ* by the reaction of the corresponding acids of formulae (VIII) and (IX), respectively, with a coupling reagent such as 1,1'-carbonyldiimidazole, dicyclohexylcarbodiimide or diphenylphosphorylazide.

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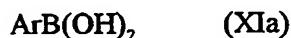
The conditions under which the activated carboxylic acid derivatives of formulae (VI) and (VII) are formed and subsequently reacted with the anilines of formulae (II) and (V), respectively, will depend upon the nature of the activated derivative. However, in general the reaction between the compounds (II) and (VI), or (V) and (VII), may be carried out in a non-aqueous medium such as, for example, dimethylformamide, tetrahydrofuran, acetonitrile or a halohydrocarbon such as dichloromethane at a temperature within the range -25°C to +120°C. The reaction may optionally be carried out in the presence of a base such as triethylamine or pyridine and the base may also be used as the solvent for reaction.

Where acid chlorides are used, the reaction may be carried out using the Schotten-Baumann technique in the presence of a suitable base, for example, aqueous sodium hydroxide, conveniently at a temperature between 0°C and 100°C, for example, room temperature.

According to another general process (3A), the compounds of general formula (I) may be prepared by treating a compound of formula (Xa)

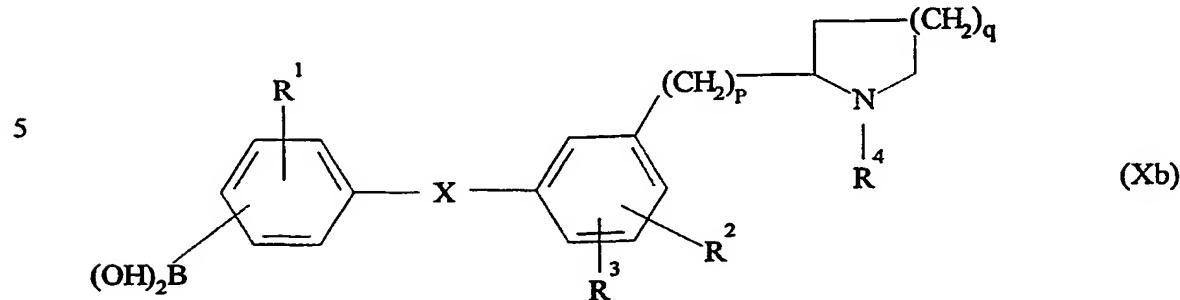


(where Y represents a bromine or iodine atom or the group  $-\text{OSO}_2\text{CF}_3$ ) with a compound of formula (XIa)



or an ester, an anhydride or a salt (e.g. lithium) thereof.

Alternatively, according to the general process (3B), the compounds of general formula (I) may be prepared by treating a compound of formula (Xb)



10 or an ester, an anhydride or a salt (e.g. lithium) thereof, with a compound of formula (XIb)



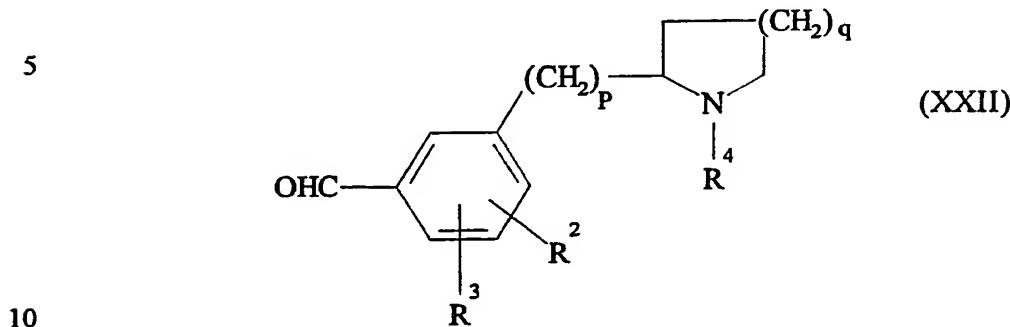
where Y represents a bromine or iodine atom or the group  $-\text{OSO}_2\text{CF}_3$ .

15 Both reactions may be effected in the presence of a transition metal catalyst such as  $(\text{Ph}_3\text{P})_4\text{Pd}$  (where Ph represents phenyl) in a suitable solvent such as an ether (e.g. 1,2-dimethoxyethane or tetrahydrofuran) in the presence or absence of water, or an aromatic hydrocarbon (e.g. benzene). The reaction is preferably carried out in the presence of a base such as an alkali or alkaline earth metal carbonate (e.g. sodium carbonate) at a suitable temperature up to reflux.

20 According to another general process (4), the compounds of general formula (I) in which X represents either of the groups  $-\text{NHCH}_2-$  or  $-\text{CH}_2\text{NH}-$  may be prepared by reduction of the corresponding compounds of general formula (I) in which X represents the groups  $-\text{NHCO}-$  or  $-\text{CONH}-$ , respectively, except that the reaction cannot be used to prepare compounds in which the group Ar contains another group reducible under the reaction conditions, for example,  $\text{CONR}^6\text{R}^7$ ,  $\text{CONR}^6(\text{CH}_2)_m\text{CO}_2\text{R}^7$ ,  $\text{SO}_2\text{R}^6$ ,  $\text{CO}_2\text{H}$ ,  $\text{COR}^6$ ,  $\text{SOR}^6$ ,  $\text{CN}$ ,  $\text{NO}_2$  or  $-(\text{CH}_2)_n\text{OC}(\text{O})\text{C}_{1-4}\text{alkyl}$ .

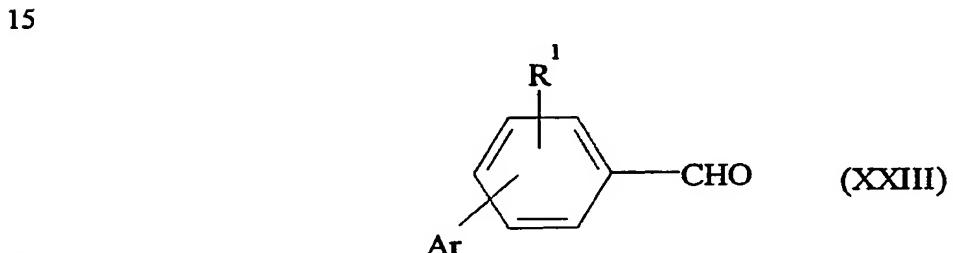
25 The reduction may be effected using a suitable metal hydride such as lithium aluminium hydride in a solvent e.g. an ether (such as tetrahydrofuran) at a temperature in the range of  $-10^\circ\text{C}$  to  $+100^\circ\text{C}$ .

According to another general process (5A), the compounds of general formula (I) in which X represents the group  $-\text{NHCH}_2-$  may be prepared by reacting an aniline of formula (V) with an aldehyde of formula (XXII)



under reducing conditions.

Alternatively, according to general process (5B), the compounds of general formula (I) in which X represents the group  $-\text{CH}_2\text{NH}-$  may be prepared by reacting an aniline of formula (II) with an aldehyde of formula (XXIII)



under reducing conditions.

Both reactions may conveniently take place in the presence of a solvent such as or an alcohol e.g. methanol or ethanol using for example a hydride reducing agent such as an alkali or alkaline earth metal borohydride (e.g. sodium borohydride or sodium cyanoborohydride). The reactions may be carried out at a temperature in the range from 0° to 60°C, conveniently at room temperature.

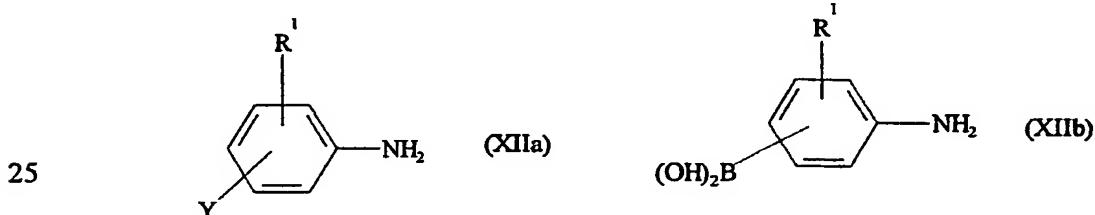
Compounds of general formula (I) in which R<sup>2</sup>, R<sup>3</sup> or substituents on the group Ar have a particular meaning may be converted into another compound of the invention by standard methods of interconversion.

For instance, when  $R^2$  and/or  $R^3$  represents a hydroxy or alkoxy group, these groups may be interchanged by standard methods of O-alkylation or O-dealkylation. Thus, for example, a compound in which  $R^2$  represents hydroxy may be prepared by treating a corresponding compound in which  $R^2$  represents methoxy with a reagent system capable of removing the methyl group e.g. a mercaptide such as sodium ethylmercaptide in a solvent such as dimethylformamide, lithium iodide in collidine, boron tribromide in a halohydrocarbon solvent e.g. methylene chloride or molten pyridine hydrochloride.

When Ar contains a hydroxymethyl group this may be converted by oxidation into a corresponding compound of general formula (I) in which Ar contains a group  $COR^6$  (where  $R^6$  is a hydrogen atom) or  $CO_2H$ . Thus, for example, oxidation may be effected using a suitable oxidising agent such as a manganese oxidising agent (e.g. manganese dioxide) in a solvent such as an ether (e.g. 1,4-dioxan) at a suitable temperature up to reflux, a chromium oxidising agent (e.g. Jones reagent) or pyridinium dichromate in a suitable solvent such as a halohydrocarbon (e.g. methylene chloride).

When Ar contains an aldehyde group this may be converted by oxidation into a corresponding compound of general formula (I) in which Ar contains a group  $CO_2H$ . Thus, for example, oxidation may be effected using a suitable oxidising agent such as a source of silver (I) (e.g. silver nitrate) in aqueous alkali optionally in the presence of a cosolvent such as an alcohol (e.g. methanol).

Intermediates of formula (V) may be prepared by reaction of a compound of formula (XIa) or (XIb) with a compound of formula (XIIa) or (XIIb), respectively,

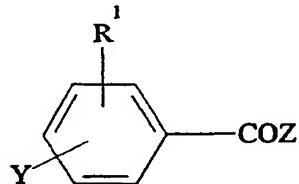


according to the method of general process (3).

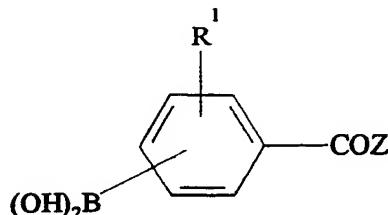
Intermediates of formula (II) or (V) may also be prepared from the corresponding carboxylic acid of formula (IX) or (VIII), respectively, using conventional procedures (e.g. by Curtius rearrangement).

Intermediates of formula (Xa) and (Xb), in which X is -CONH-, may be prepared by reaction of a compound of formula (II) with a compound of formula (XIIIa) or (XIIIb), respectively,

5



(XIIIa)



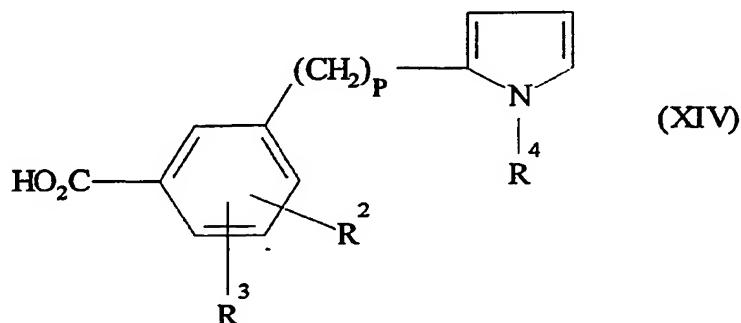
(XIIIb)

10 according to the method of general process (2).

Intermediates of formulae (Xa) and (Xb), in which X is -NHCO-, may be prepared by reaction of a compound of formula (VII) with a compound of formula (XIIIa) or (XIIIb), respectively, according to the method of general process (2).

15 Intermediates of formula (IX) in which q is 1 may be prepared by reducing a compound of formula (XIV)

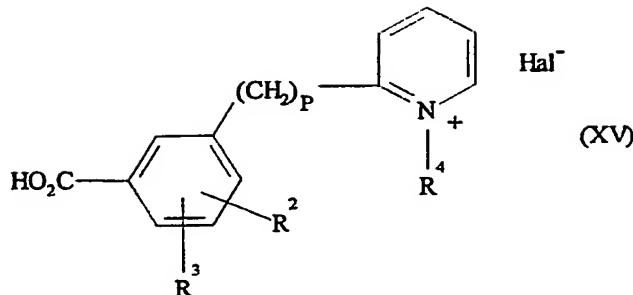
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Similarly, intermediates of formula (IX) in which q is 2 may be prepared by reducing a salt 25 of formula (XV)

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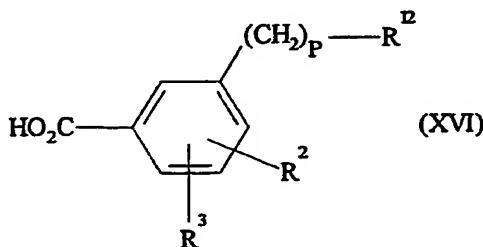
(wherein  $\text{Hal}^-$  is a halide ion e.g. an iodide ion).

These reductions may be effected under standard conditions of hydrogenation e.g. using hydrogen in the presence of a catalyst such as palladium or platinum or oxides thereof. The reaction may be carried out at any suitable temperature, for example, from 10  $0^\circ$  to  $100^\circ\text{C}$ , conveniently at room temperature, and preferably in a solvent. Suitable solvents include alcohols (e.g. ethanol), ethers (e.g. dioxan or dimethoxyethane), amides (e.g. dimethylformamide) or esters (e.g. ethyl acetate) or a mixture of solvents (e.g. ethanol/dimethylformamide).

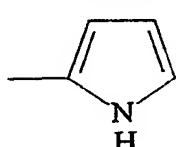
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The compounds of formulae (XIV) and (XV) may be prepared from compounds of formula (XVI)

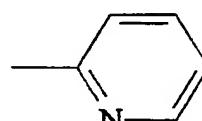
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25 (where  $\text{R}^{12}$  represents



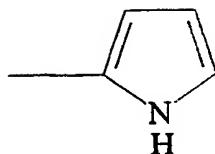
and



, respectively

30

Thus, compounds of formula (XIV) may be prepared from compounds of formula (XVI) where  $\text{R}^{12}$  represents



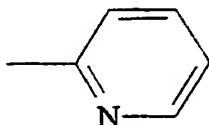
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by treating the compound of formula (XVI) with, for example, an alkali metal amide such as potassium amide or sodium amide in liquid ammonia, an alkali metal hydride such as sodium hydride or potassium hydride in a suitable solvent such as an ether (e.g. tetrahydrofuran) or an amide (e.g. dimethylformamide) or with n-butyllithium in hexane, followed by an alkylation step using a halide  $R^4 Hal$  (where Hal is a halogen atom e.g. chlorine, bromine or iodine) in a suitable solvent such as an ether (e.g. dimethoxyethane) or an amide (e.g. dimethylformamide).

10

Compounds of formula (XV) may be prepared from compounds of formula (XVI) where  $R^{12}$  is

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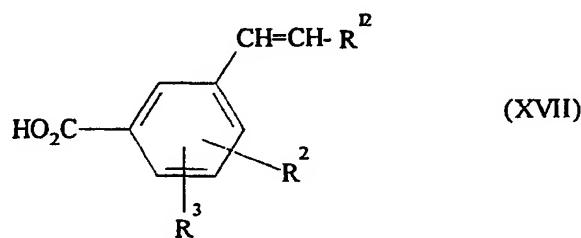


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by reaction with a halide  $R^4 Hal$  (where Hal is chlorine, bromine or iodine), in a suitable solvent such as a ketone (e.g. acetone), a nitrile (e.g. acetonitrile) or an alcohol (e.g. ethanol).

Intermediates of formula (XVI) in which  $p$  is 2 may be prepared by reducing a compound of formula (XVII)

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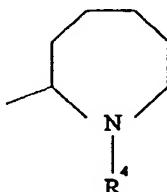


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(where  $R^{12}$  is as defined in formula (XVI) above).

Additionally, intermediates of formula (IX) where  $p$  is 2 and  $q$  is 3 may be prepared by reducing a compound of formula (XVII) where  $R^{12}$  represents

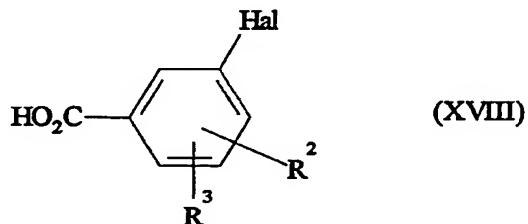
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10 The reduction of compounds of formula (XVII) may be effected using hydrogen and a metal catalyst such as palladium or platinum or oxides thereof in a suitable solvent.

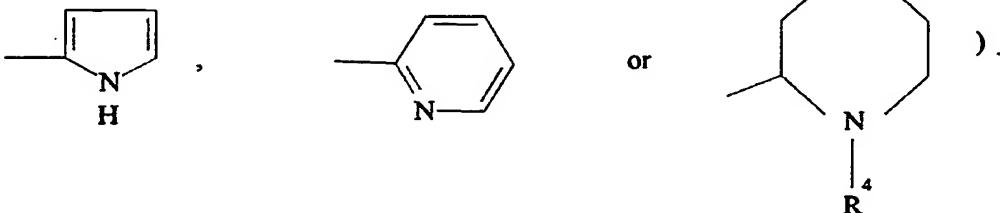
Compounds of formula (XVII) may be prepared from a compound of formula (XVIII)

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(where Hal is bromine or iodine) by reaction with an appropriate alkene of formula  $CH_2=CH-R^{12}$  (where  $R^{12}$  represents

20



25

The reaction may be effected in the presence of a palladium reagent such as palladium acetate and preferably in the presence of a base such as a tertiary amine e.g. triethylamine. The reaction may be effected in the presence or absence of a solvent. Suitable solvents include nitriles (e.g. acetonitrile), amides (e.g. dimethylformamide) and water.

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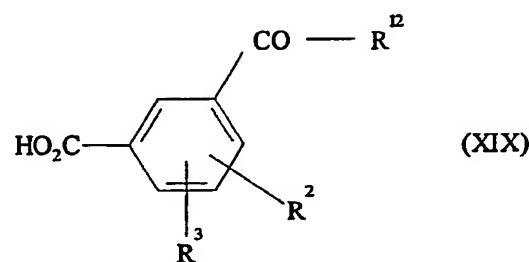
Intermediates of formula (XVI) in which  $R^{12}$  represents



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and p is 1 may be prepared by reducing a compound of formula (XIX)

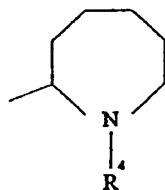
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(where R<sup>12</sup> is as defined in formula (XVI) above).

Intermediates of formula (IX) where p is 1 and q is 3 may be prepared by reducing a compound of formula (XIX) where R<sup>12</sup> is

15

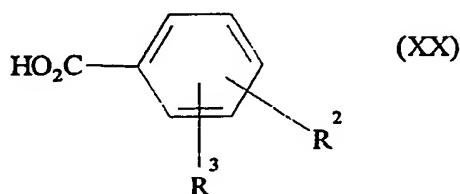


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The reduction of compounds of formula (XIX) may be effected using hydrogen and a metal catalyst such as palladium or platinum or oxides thereof or using hydrazine hydrate and a base (e.g. an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide).

Compounds of formula (XIX) may be prepared from a compound of formula (XX)

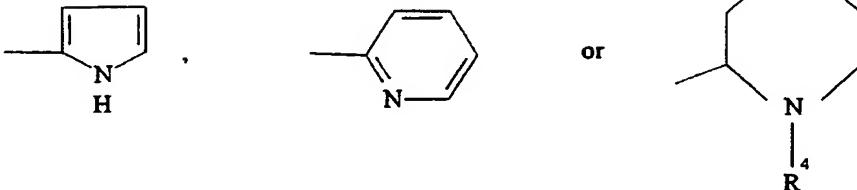
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by a Friedel Craft reaction involving an acyl halide of the formula  $\text{Hal}-\text{CO}-\text{R}^{12}$  (where  $\text{R}^{12}$  represents

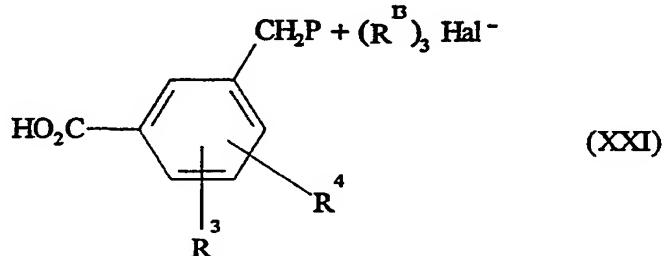
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and  $\text{Hal}$  represents chlorine or bromine) with the proviso that at least one of the positions  
10 on the phenyl ring meta in relation to the carboxyl group is unoccupied.

Alternatively, intermediates of formula (XVII) may be prepared by the reaction of a phosphonium salt of a halide of formula (XXI)

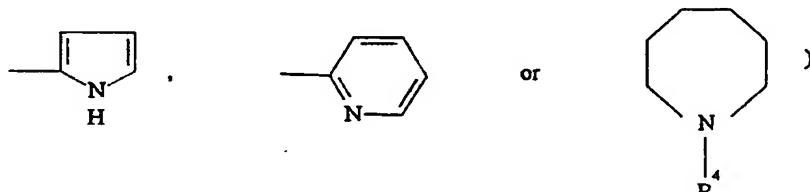
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(where  $\text{Hal}^-$  represents a halide (e.g. chloride) ion and  $\text{R}^{13}$  represents, for example, an aryl or alkoxy group) with an aldehyde of the formula  $\text{R}^{12}\text{CHO}$  (where  $\text{R}^{12}$  represents

25



in the presence of a suitable strong base such as an alkoxide (e.g. potassium t-butoxide) and in the presence of a suitable solvent such as an ether (e.g. tetrahydrofuran) at ambient temperature.

30

Suitable phosphonium salts include aryl phosphonium salts such as triphenylphosphonium salts (where R<sup>13</sup> represents an aryl group) which may be prepared according to established procedures.

It will be appreciated that, where necessary, a halogen substituent may be converted 5 into a carboxyl group using standard methodology thus, for example, compounds of formula (VIII) or (IX) may be prepared from an intermediate of formula (III) or (IV), respectively, by lithiation using, for example, n-butyl lithium followed by quenching with carbon dioxide.

10 The boronic acid intermediates of formulae (Xb), (XIa), (XIIb) and (XIIIb) or their esters, anhydrides or salts may be used *in situ* under the conditions described above for general process (3).

The aldehydes of formula (XXII) or (XXIII) may be prepared from an intermediate of formula (IV) or (III), respectively, by lithiation using, for example, n-butyl lithium followed by formylation using, for example, dimethylformamide.

15 Intermediates of formulae (III), (XIa), (XIb), (XIIa), (XIIb), (XIIIa), (XIIIb), (XVIII) and (XX) are either known compounds or may be prepared by standard methodology or methods analogous to those described herein.

20 Physiologically acceptable acid addition salts of the compounds of general formula (I) may be prepared by treating the corresponding free base with a suitable acid using conventional methods. Thus, for example, a generally convenient method of forming the acid addition salts is to mix appropriate quantities of the free base and the acid in an appropriate solvent e.g. an alcohol such as ethanol or an ester such as ethyl acetate.

25 Inorganic basic salts of compounds of general formula (I) may be prepared by treating the corresponding acid of general formula (I) (i.e. a compound of general formula (I) in which Ar contains the group CO<sub>2</sub>H) with a suitable base using conventional methods.

Salts of compounds of general formula (I) may also be converted into different 30 physiologically acceptable salts of compounds of general formula (I) using conventional methods.

The invention is illustrated but not limited by the following examples in which temperatures are in °C. Thin layer chromatography (T.l.c.) was carried out on silica plates. 'Dried' refers to drying using sodium sulphate or magnesium sulphate unless otherwise stated. Flash column chromatography (FCC) was carried out on silica gel (Merck 9385) unless otherwise stated. Short path column chromatography (SPC) was carried out on silica gel (Merck 7747) unless otherwise stated.

The following solvent systems were used: System A - dichloromethane:ethanol:0.88 ammonia; System B - dichloromethane:methanol; System C - hexane:diethyl ether.

The following abbreviations are used: ether - diethyl ether; THF - tetrahydrofuran; DME - 1,2-dimethoxyethane; DMF - dimethylformamide.

#### Intermediate 1

##### [4-[Bis(phenylmethyl)amino]phenyl]boronic acid

n-Butyllithium (1.60M in hexane, 98ml) was added dropwise under nitrogen to a stirred solution of N-(4-bromophenyl)-N-(phenylmethyl)benzenemethanamine (50.0g) in dry THF (500ml) at -67 to -65° over 30 min. After 1h, triisopropylborate (57ml) was added dropwise over 20min and the mixture stirred at 23° for 16h. Water (80ml) was added, the mixture was evaporated, and then co-evaporated with ethanol (2x100ml). The residue was treated with dichloromethane (200ml) and the slurry purified by FCC using gradient elution with a gradient of System B (1:0) to (97:3) to afford the title compound (5.6g) as fine cream crystals.

T.l.c. System B (50:1) Rf 0.16.

#### Intermediate 2

##### 1-[4-[Bis(phenylmethyl)amino][1,1'-biphenyl]-4-yl]ethanone

A hot solution of Intermediate 1 (4.00g) and 1-(4-bromophenyl)ethanone (2.51g) in DME (110ml) was treated with tetrakis(triphenylphosphine)palladium (0) (0.58g) followed by a solution of sodium carbonate (1.34g) in water (55ml) and then stirred at reflux under nitrogen for 1.25h. The cooled mixture was evaporated, treated with aqueous 2M sodium carbonate (150ml), and extracted with ethyl acetate (4x200ml). The

combined, dried, organic extracts were evaporated and the residue was crystallised from ethyl acetate to give a crop of the title compound (3.76g). The mother liquors were concentrated to give a second crop of the title compound (0.66g). The combined crops were purified by FCC eluting with System C (9:1 to 7:3) to give the title compound (2.01g) as fine cream-coloured crystals m.p. 140-143°C.

Similarly prepared was:-

Intermediate 3

10 4'-(Bis(phenylmethyl)amino)[1,1'-biphenyl]-4-carboxamide (6.44g) as fine white needles, m.p. 199-200.5°.

From Intermediate 1 (8.00g) and 4-bromobenzamide (5.04g) except that the residue was suspended in 1M sodium carbonate (150ml), the solid filtered off, dried and treated with refluxing acetonitrile (600ml). The mixture was then filtered, the filtrate heated to reflux and the precipitate, which resulted upon cooling, filtered off. The mother liquors were evaporated and the residue crystallised from acetonitrile to give a further crop of the title compound (1.78g).

Intermediate 4

20 4'-Amino[1,1'-biphenyl]-4-carboxamide

A solution of Intermediate 3 (7.75g) in dry THF (200ml) was added to a mixture of pre-reduced 10% palladium oxide-on-carbon (3.00g) and the stirred suspension hydrogenated at room temperature and pressure until uptake ceased. The catalyst was filtered off, the filtrate evaporated, and a solution of the residue in DMF (150ml) was added to a mixture of pre-reduced 10% palladium oxide-on-carbon (2.00g) in ethanol (25ml). The stirred suspension was hydrogenated at room temperature and pressure until uptake ceased. The catalyst was filtered off and the filtered pad washed with hot ethanol. The filtrate and washings were evaporated to give a solid (4.00g). A portion of the solid (500mg) was recrystallised from acetonitrile to give the pure title compound (56mg) as fine light grey crystals, m.p. 281-284°.

Intermediate 54'-Amino- $\alpha$ -methyl[1,1'-biphenyl]-4-methanol

A solution of Intermediate 2 (1.80g) in dry THF (22ml) was added to a suspension of 5 10% palladium oxide-on-carbon (0.9g) in dry THF (15ml) and the stirred mixture hydrogenated at room temperature and pressure. The catalyst was filtered off and the filtrate evaporated and purified by FCC. Elution with System C (3:10:1) afforded the title compound (645mg) as fine white crystals, m.p. 111-115°.

10 Intermediate 6

[4-[[[(1,1-Dimethylethyl)dimethylsilyloxy]phenyl]boronic acid, bimolecular anhydride] n-Butyl lithium (1.6M; 9.7ml) was added, over 8 min, under nitrogen to a stirred, cooled (-70°) solution of 1-bromo-4-[[[(1,1-dimethylethyl)dimethylsilyloxy]benzene (4g) in dry THF (40ml). After a further 25 min, the resulting solution was added over 10 min to a stirred cooled (-66°) solution of tri-isopropyl borate (10ml) in THF (40ml) and the mixture stirred at room temperature for 2h. Water (10ml) and, after a further 5 min, pH 6.5 phosphate buffer (100ml) and ether (50ml) were added and the mixture stirred vigorously for 10 min. The aqueous layer was extracted with ether (2x70ml) and the combined organic solutions dried and evaporated in vacuo to leave a white solid. 15 Crystallisation from ether gave the title compound (2.02g) as a white solid m.p. 193-7°. 20 T.l.c. (dichloromethane:methanol, 96:4) Rf 0.56.

Intermediate 7(4-Formyl-2-methylphenyl)boronic acid

25 A stirred solution of 2,5-dibromotoluene (5.00g) in dry THF (200ml) under nitrogen at -78° was treated dropwise with n-butyllithium (11.8ml, 1.69M in hexane). After 1h, DMF (1.6ml) was added and the mixture was allowed to warm to 0° and then recooled to -78° and treated with more n-butyllithium (11.8ml, 1.69M in hexane). After 1h, triisopropylborate (7.0ml) was added and the cooling bath removed. After 1h, 2N 30 hydrochloric acid (80ml) was added and the THF removed under vacuum. The residue

was extracted with ether (3 x 100ml) and the combined extracts were dried and evaporated to give an oil. SPC (Merck 7729) using chloroform:ethanol (50:1) as eluent gave the product (2.21g) as an almost colourless oil. Addition of acetone (50ml) and water (50ml) and evaporation to dryness gave the title compound (1.31g) as a colourless solid.

T.l.c. (chloroform:ethanol 50:1) Rf 0.25.

### Intermediate 8

#### (4-Acetylphenyl)boronic acid

n-Butyllithium (81.6ml) was added dropwise to a stirred solution of 2-(4-bromophenyl)-2-methyl-1,3-dioxolane (30.0g) in dry THF (400ml), under nitrogen, at -75°C. After a period of 1.5h, triisopropylborate (31.2ml) was added dropwise at -75°C. The reaction was allowed to warm to room temperature over a 3h period. Hydrochloric acid (2N; 200ml) was added and the reaction was allowed to stand at room temperature overnight. The solvent was evaporated and the residue was purified by FCC eluting with ether to give a white solid which was purified by crystallisation from water (200ml) to give the title compound (14.52g) as a white crystalline solid, m.p. 268-270°C.

### Intermediate 9

#### (E)-4-Methoxy-3-[2-(2-pyridinyl)ethenyl]benzoic acid

A mixture of 3-iodo-4-methoxybenzoic acid (2.0g), 2-ethenylpyridine (1.0ml), triethylamine (2.5ml), acetonitrile (3.3ml) and palladium acetate (0.15g) was heated at 115-120° for 48h. The reaction mixture was filtered through celite, and the pad was washed with ethyl acetate (50ml). The filtrate was extracted with saturated aqueous sodium bicarbonate solution (50ml), and the aqueous layer was washed with ethyl acetate (2x50ml). The aqueous extract was neutralised using 2N hydrochloric acid resulting in the formation of a cream- coloured precipitate. The precipitate was removed and dried in vacuo. Recrystallisation from ethanol gave the title compound (0.68g) as a white microcrystalline solid, m.p. 187-191°.

The mother liquors were evaporated in vacuo, and the resulting solid was recrystallised from ethanol to give the title compound (0.47g).

T.l.c. (cyclohexane-ethyl acetate-acetic acid, 1:2:0.05) Rf 0.26.

5      Intermediate 10

4-Methoxy-3-[2-(2-pyridinyl)ethyl]benzoic acid

Intermediate 9 (98mg) was dissolved in glacial acetic acid (5ml). This solution was added to a pre-reduced suspension of 10% palladium oxide on carbon (50% aqueous paste, 40mg) in glacial acetic acid (4ml) and the mixture was stirred under 1 atmosphere of hydrogen for 90 min. The catalyst was removed by filtration through celite, and the filtrate was evaporated in vacuo to give an off-white solid. The solid was crystallised from ethanol to give the title compound (80mg) as a white microcrystalline powder, m.p. 193-6°.

15      Intermediate 11

4-Methoxy-3-[2-(1-methyl-2-piperidinyl)ethyl]benzoic acid, hydroiodide

Intermediate 10 (200mg) was dissolved in DMF (10ml) and methyl iodide (0.2ml) was added. The mixture was kept at room temperature for 70h. Further methyl iodide (0.1ml) was added, and the mixture kept at room temperature for 22h. A further portion of methyl iodide (0.1ml) was added and the mixture was kept at room temperature for 20h. The solution was evaporated in vacuo and Adams catalyst (25mg) was added. The mixture was hydrogenated at 50 psi for 6h. The catalyst was removed by filtration through Celite and the solvent was evaporated in vacuo. Re-evaporation with ethyl acetate, followed by trituration with ethyl acetate gave the hydroiodide of the title compound as a white powder (282mg). Purification of a sample of the hydroiodide by FCC eluting with isopropanol:ether:water:aqueous ammonia (20:20:8:1) gave the title compound as a white solid, m.p. 162 -165°.

Intermediate 12

30      N-(4-Bromophenyl)-4-methoxy-3-[2-(1-methyl-2-piperidinyl)ethyl] benzamide

Intermediate 11 (1.6g) was treated with thionyl chloride (5ml) and stirred at reflux for 20min. When cool, the solution was evaporated and then co-evaporated with toluene (2x10ml). The residue was treated with 4-bromobenzenamine (967mg), followed by pyridine (5ml) and then stirred at 110° under nitrogen for 3h. When cool, aqueous saturated sodium bicarbonate (30ml) was added and the mixture evaporated. The residue was purified by SPC using System A (97:3:0.5) to give the title compound as a cream coloured solid which was recrystallised from ethanol (1.7g) m.p. 152-154°C.

Intermediate 13

10 N-(4-Bromophenyl)-4-hydroxy-3-[2-(1-methyl-2-piperidinyl)ethyl] benzamide

A solution of sodium ethanethiolate was prepared by adding ethanethiol (1ml) slowly dropwise to a stirred suspension of sodium hydride (544mg of a 60% w/w dispersion) in dry DMF (8ml). After stirring for 1h the solution was treated with a solution of Intermediate 12 (730mg) in warm dry DMF (8ml). The resulting solution was heated in an oil bath (150°, 6h), cooled and evaporated to dryness. The residue was partially purified by SPC using System A (189:10:1) and then further purified by HPLC to give the title compound (520mg) as a cream-coloured foam.

Analysis Found: C,60.4; H,5.9; N,6.4; Br, 19.2.

C<sub>21</sub>H<sub>25</sub>N<sub>2</sub>BrO<sub>2</sub> requires C,60.4; H,6.0; N,6.7; Br, 19.15%

20

Intermediate 14

4-Methoxy-3-[2-(1-propyl-2-piperidinyl)ethyl]benzoic acid

Intermediate 10 (885mg) was dissolved in DMF (100ml) and iodopropane (2.7ml) was added. The reaction was stirred at 120°C for 24h. The solution was then evaporated to dryness to give an orange coloured solid, which was subsequently dissolved in methanol (100ml), and passed down an Amberlyst A-26 (Cl<sup>-</sup>) ion exchange column. The methanolic fractions were combined and evaporated to dryness to give a cream coloured solid, which was dissolved in further methanol (100ml). Adam's catalyst was added (160mg) and the resulting suspension was hydrogenated at 50 psi for 18h. The catalyst was removed by filtration and the filtrate evaporated in vacuo to give a solid-like residue.

The residue was purified by SPC using System A (67:30:3), to give a yellow foamy solid which on trituration with ethyl acetate gave the title compound (702mg) as a white solid m.p. 211-214°C.

5      Intermediate 15

N-(4-Bromophenyl)-4-methoxy-3-[2-(1-propyl-2-piperidinyl)ethyl]benzamide

Intermediate 14 (750mg) was treated with thionyl chloride (5ml) and stirred at reflux for 35min. When cool, the solution was evaporated and then co-evaporated with toluene (2x25ml). The residue was treated with 4-bromobenzenamine (418mg), followed by 10 pyridine (7ml) and stirred at 110° under nitrogen for 3.5h. When cool, aqueous saturated sodium bicarbonate (60ml) was added and the mixture evaporated. The residue was purified by SPC using System A (97:3:0.3) to give the title compound (741mg) as a cream-coloured foam, m.p. 97-99°C.

15      Example 1

N-[[4'-Aminosulphonyl][1,1'biphenyl]-4-yl]-3-[2-(1-methyl-2-piperidinyl)ethyl]-4-methoxybenzamide, oxalate

Intermediate 11 (291mg) was dissolved in pyridine (5ml) in a nitrogen atmosphere. The solution was cooled in an ice-bath, and thionyl chloride (0.10ml) was added. The mixture 20 was warmed to room temperature and stirred for 1h. The reaction mixture was cooled in an ice-bath and a solution of 4'-amino-[1,1'-biphenyl]-4-sulphonamide (278mg) in pyridine (5ml) was added. The mixture was stirred at room temperature for 16h. The solvent was evaporated in vacuo to give a purple gum, which was dissolved in System A (100:8:1) and purified by FCC. Elution using the same solvent system gave the free base of the title 25 compound (363mg) as a pale brown solid. A portion of the free base (260mg) was suspended in methanol (45ml) and oxalic acid (47mg) was added to give a clear solution. This solution was evaporated in vacuo to give a pink gum which was dissolved in methanol (3ml). Ether (80ml) was added and the mixture was stirred at room temperature for 6h to give the title compound (286mg) as a pink solid,

30      T.l.c. System A (50:8:1) Rf 0.43.

n.m.r. (DMSO-d<sub>6</sub>) δ 1.3-2.1(8H,m), 2.6-3.4(5H,m), 2.76(3H,s), 3.92(3H,s), 7.15 and 7.75-8.0(11H,m), 7.43(2H,brs), 10.3 (1H,s).

Example 2

5 N-[[4'-Aminocarbonyl][1,1'-biphenyl]-4-yl]-3-[2-(1-methyl-2-piperidinyl)ethyl]-4-methoxybenzamide, oxalate

Intermediate 11 (1.321g) was dissolved in dry pyridine (25ml) in a nitrogen atmosphere. The resulting solution was cooled in an ice-bath and thionyl chloride (0.45ml) was added dropwise to give a dark solution. The reaction mixture was stirred at room temperature for 1h. The mixture was re-cooled in an ice-bath, and Intermediate 4 (1.08g) was added portionwise, followed by dry pyridine (25ml). The reaction mixture was stirred at room temperature for 18h, and evaporated in vacuo to give a brown oil. This was dissolved in System A (50:8:1) and purified by FCC eluting with the same solvent system to give a brown solid. This solid was purified by HPLC to give the free base of the title compound (54mg). The free base (52mg) was suspended in methanol (6ml) and oxalic acid (10mg) was added to give a clear solution. The solvent was evaporated in vacuo to give a cream-coloured solid which was re-suspended in methanol (1ml). Ether (50ml) was added and the mixture was stirred at room temperature for 3h to give the title compound (47mg) as a cream-coloured solid.

20 T.l.c. System A (50:8:1) R<sub>f</sub> 0.31.

Analysis      Found:      C,63.7; H,6.3; N,7.3.

C<sub>29</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub>.1.4C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> requires      C,63.9; H,6.0; N,7.0%.

Example 3

25 N-[4'-(1-Hydroxyethyl)[1,1'-biphenyl]-4-yl]-4-methoxy-3-[2-(1-methyl-2-piperidinyl)ethyl]benzamide

Intermediate 11 (0.5g) was treated with thionyl chloride (2ml) and stirred at reflux for 15min. When cool, the solution was evaporated and then co-evaporated with toluene (2x10ml). The residue was treated with Intermediate 5 (0.339g), followed by pyridine (4ml) and then stirred at 100-110° under nitrogen for 4h. When cool, aqueous saturated

sodium bicarbonate (40ml) was added and the mixture evaporated. The residue was purified by SPC eluting with System A (97:25:0.5) to give the title compound (0.421g) as an off-white solid, m.p. 202-204°C.

Analysis Found: C,76.6; H,7.8; N,5.9.

5 C<sub>30</sub>H<sub>36</sub>N<sub>2</sub>O<sub>3</sub> requires C,76.2; H,7.7; N,5.9%.

Similarly prepared was :-

Example 4

10 4'-[[4-Methoxy-3-[2-(1-methyl-2-piperidinyl)ethyl]benzoyl]amino][1,1'-biphenyl]-4-carboxylic acid (230mg) m.p. 240-242°C.

Analysis Found: C,70.45; H,7.0; N,5.5.

C<sub>29</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>.1.0H<sub>2</sub>O.0.25C<sub>2</sub>H<sub>5</sub>OH requires C,70.6; H,7.1; N,5.6%.

Water Assay Found: 3.74% w/w H<sub>2</sub>O=1.0mol H<sub>2</sub>O

15 From Intermediate 11 (1g) and 4'-amino[1,1'-biphenyl]-4-carboxylic acid (679mg) with a reaction time of 18h and purification by SPC eluting with System A (60:38:2).

Example 5

N-(4'-Acetyl[1,1'-biphenyl]-4-yl)-4-methoxy-3-[2-(1-methyl-2-piperidinyl)ethyl]

20 benzamide

A solution of the product of Example 3 (200mg) in dry 1,4-dioxan (12ml) was treated with activated manganese (IV) oxide (184mg) and the mixture stirred at reflux for 6h. The mixture was filtered, and the filter cake washed with hot ethanol. The combined filtrate and washings were evaporated and the residue purified by SPC. Elution with System A (97:3:0.3) afforded the title compound (147mg) as a white crystalline solid, m.p. 219-222°C.

Analysis Found: C,75.6; H,7.2; N,5.7.

C<sub>30</sub>H<sub>34</sub>N<sub>2</sub>O<sub>3</sub>.0.34 H<sub>2</sub>O requires C,75.6; H,7.3; N,5.9%.

Water Assay Found: 1.26% w/w H<sub>2</sub>O=0.34mol H<sub>2</sub>O

Example 64'-[[[4-Methoxy-3-[2-(1-methyl-2-piperidinyl)ethyl]phenyl]methyl]amino]- $\alpha$ -methyl  
[1,1'-biphenyl]-4-methanol

A solution of the product of Example 3 (150mg) in dry THF (7ml) was added over 2 min  
5 to a stirred slurry of lithium aluminium hydride (36mg) in dry THF (7ml) under nitrogen,  
and the mixture heated under reflux for 2h. When cool, water (2ml) in THF (5ml) was  
added dropwise over 5 min with ice-cooling and the resultant mixture filtered, washing  
the precipitate with THF (50ml). The filtrate was concentrated to give an off-white solid  
which was purified by SPC eluting with System A (97.5:2.5:0.5) to give the title  
10 compound (120mg) as a white foam-like solid.

Analysis Found: C,77.9; H,8.4.; N,5.7.

C<sub>30</sub>H<sub>38</sub>N<sub>2</sub>O<sub>2</sub>·0.27H<sub>2</sub>O requires C,77.7; H,8.4; N,6.0%.

Water assay Found: 1.04% w/w H<sub>2</sub>O=0.27mol H<sub>2</sub>O

n.m.r. (250MHz, CDCl<sub>3</sub>) δ 1.2 - 2.2 (14H, m), 2.29 (3H, s), 2.48 - 2.78 (2H, m), 2.86  
15 (1H, ddd), 3.8 (3H, s), 4.03 (1H, t), 4.28 (2H, d), 4.93 (1H, q), 6.7 (2H, 1/2 AA'BB'),  
6.82 (1H, d), 7.15 - 7.22 (2H, dd + d), 7.38 - 7.48 (4H, 2 x 1/2 AA'BB'), 7.53 (2H, 1/2  
AA'BB').

Example 7N-(4'-Acetyl[1,1'-biphenyl]-4-yl)-4-hydroxy-3-[2-(1-methyl-2-piperidinyl)ethyl]  
benzamide

A catalytic quantity of tetrakis(triphenylphosphine)palladium (0) (23mg) was added to a  
degassed mixture of Intermediate 13 (209mg), Intermediate 8 (90mg), and sodium  
carbonate (58mg) in DME (5ml) and water (2ml). The reaction mixture was heated at  
25 reflux for 24h and was then partitioned between aqueous sodium carbonate (2N; 50ml)  
and dichloromethane (50ml). The separated aqueous fraction was further extracted with  
dichloromethane (3x50ml) and the combined extracts were dried, filtered and the filtrate  
adsorbed onto silica (Merck 7734, 5g). The residue was purified by SPC eluting with  
System A (189:10:1) to give a yellow solid (145mg). The solid was crystallised from  
30

toluene (6ml) to give the title compound (70mg) as an off-white solid, m.p. 198.5-200.5°C.

Analysis Found: C,75.8; H,7.0; N,5.9.

$C_{29}H_{32}N_2O_3 \cdot 0.06H_2O$  requires C,76.1; H,7.1; N,6.1%.

5 Water Assay Found: 0.25% w/w  $H_2O = 0.06\text{mol } H_2O$ .

Example 8

4-Hydroxy-N-(4'-hydroxy[1,1'-biphenyl]-4-yl)-3-[2-(1-methyl-2-piperidinyl)ethyl]benzamide

10 A catalytic quantity of tetrakis(triphenylphosphine)palladium (0) (25mg) was added to a degassed mixture of Intermediate 13 (150mg), the free acid of Intermediate 6 (108mg), and sodium carbonate (46mg) in DME (3ml) and water (3ml). The reaction mixture was heated at reflux for 24h and the reaction contents adsorbed onto silica gel (Merck 7734, 3g). The residue was purified by SPC eluting with System A (95:5:0.5) to give the title compound (94mg) as a cream-coloured solid, m.p. 164-165°C  
 15 T.l.c. System A (90:10:1) Rf 0.35

Similarly prepared were:-

20 Example 9

N-(4'-Hydroxy[1,1'-biphenyl]-4-yl)-4-methoxy-3-[2-(1-propyl-2-piperidinyl)ethyl]benzamide (300mg), m.p. 115-117°C.

Analysis Found: C,73.9; H,7.6; N,5.5;

$C_{30}H_{36}N_2O_3 \cdot 0.47H_2O \cdot 0.4C_2H_5OH$  requires C,74.1; H,7.9; N,5.6%

25 Water Assay Found: 1.73% w/w  $H_2O = 0.47\text{mol } H_2O$

From Intermediate 15 (350mg) and the free acid of Intermediate 6 (237mg).

Example 10

N-(4'-Formyl-2'-methyl[1,1'-biphenyl]-4-yl)-4-methoxy-3-[2-(1-methyl-2-piperidinyl)

30 ethyl]benzamide as a yellow foam (250mg), m.p. 60-62°C (dec)

Analysis Found: C, 75.4; H, 7.4; N, 5.7.

$C_{30}H_{34}N_2O_3 \cdot 0.28 H_2O$  0.08  $CH_3CO_2C_2H_5$   
 requires C, 75.4; H, 7.3; N, 5.8%.

Water Assay Found: 1.03% w/w  $\text{H}_2\text{O}$  = 0.28 mol  $\text{H}_2\text{O}$

5 From Intermediate 12 (0.9g) and Intermediate 7 (379mg). Purification by SPC eluting with System A (98:2:0.2) afforded the **title compound**.

### Example 11

## N-(4'-Hydroxy[1,1'-biphenyl]-4-yl)-4-methoxy-3-[2-(1-methyl-2-piperidinyl)ethyl]

10 benzamide as a cream-coloured solid (68mg) m.p. 226.5-228°C

Analysis found C,74.8; H,7.5; N,6.1.

$C_{28}H_{32}N_2O_3$  0.18  $H_2O$  requires C,75.1; H,7.3; N,6.3%.

Water Analysis Found: 0.7% w/w  $\text{H}_2\text{O}$  = 0.18 mol  $\text{H}_2\text{O}$ .

15 From Intermediate 12 (164mg) and Intermediate 6 (115mg). Purification by FCC eluting with System A (95:5:0.5) afforded a cream-coloured foam. Dissolving the foam in ethyl acetate (20ml) and evaporating in vacuo transformed the foam into a beige solid, which after being triturated with ethanol gave the title compound.

### Example 12

20 N-[4-(4-Pyridinyl)phenyl]-4-methoxy-3-[2-(1-methyl-2-piperidinyl)ethyl]benzamide.

### oxalate

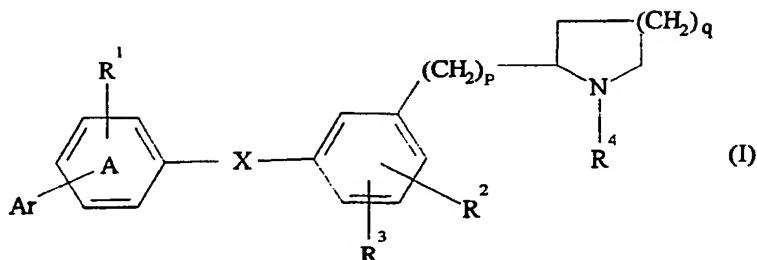
Intermediate 11 (0.991g) was dissolved in dry pyridine in a nitrogen atmosphere. The solution was cooled in an ice-water bath, and thionyl chloride (0.37ml) was added dropwise, and the mixture was warmed to room temperature to give a dark brown solution. This solution was stirred at room temperature for 1h, and re-cooled in an ice-water bath. A suspension of 4-(4-pyridinyl)benzeneamine (0.919g) in pyridine (20ml) was added dropwise, and the mixture was warmed to room temperature and stirred for 20h. The solvent was evaporated in vacuo to give a brown oil which was purified by FCC eluting with System A (100:8:1) to give the free base of the title compound as a fawn-coloured solid (0.795g) m.p. 160-162°C (dec).

The free base (700mg) was dissolved in methanol (5ml) and a solution of oxalic acid (147mg) in methanol (2ml) was added. Ether (75ml) was added, and the mixture was stirred vigorously for 3h to give the title compound as a fawn-coloured solid, (757mg) m.p. 180-185°C (dec).

5 Analysis Found: C,66.6; H,6.6; N, 7.7.  
C<sub>27</sub>H<sub>31</sub>N<sub>3</sub>O<sub>2</sub>,C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> requires C,67.0; H,6.4; N,8.0%

Claims

## 1. Compounds of the general formula (I) :-



5

or a physiologically acceptable salt or solvate thereof, in which

R<sup>1</sup> represents a hydrogen atom or a halogen atom or a C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy group;

10 R<sup>2</sup> and R<sup>3</sup> which may be the same or different, each independently represent a hydrogen atom or a halogen atom, or a hydroxy, C<sub>1-6</sub>alkoxy or C<sub>1-6</sub>alkyl group;

R<sup>4</sup> represents a hydrogen atom or a C<sub>1-6</sub>alkyl group;

Ar represents a phenyl group optionally substituted by one or two substituents selected from halogen atoms, or C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, hydroxy, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sup>5</sup>, -COR<sup>6</sup>, -SR<sup>6</sup>, -SOR<sup>6</sup>, -SO<sub>2</sub>R<sup>6</sup>, -CR<sup>6</sup>=NOR<sup>7</sup>, -CONR<sup>6</sup>R<sup>7</sup>, -CONR<sup>6</sup>SO<sub>2</sub>R<sup>7</sup>, -CONR<sup>6</sup>(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>R<sup>7</sup>, -CONR<sup>6</sup>(CH<sub>2</sub>)<sub>m</sub>O C<sub>1-4</sub>alkyl, -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, -OC(O)NR<sup>6</sup>R<sup>7</sup>, -(CH<sub>2</sub>)<sub>n</sub>NR<sup>8</sup>R<sup>9</sup>, -(CH<sub>2</sub>)<sub>n</sub>OC(O)C<sub>1-4</sub>alkyl (optionally substituted by a C<sub>1-6</sub>alkoxy group), or C<sub>1-4</sub>alkoxyalkyl (optionally substituted by a C<sub>1-4</sub>alkoxy or hydroxy group), a 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,5-oxadiazol-3-yl, imidazol-1-ylmethyl, dioxolan or thioxolan group (each of which may be optionally substituted by a C<sub>1-3</sub>alkyl group) or, when two substituents are attached to adjacent carbon atoms, they may form a 5- or 6-membered saturated fused ring which contains one or two oxygen atoms and which may be optionally substituted by an oxo group;

25 or Ar represents a pyridinyl group optionally substituted by one or two substituents selected from halogen atoms, C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, hydroxy, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sup>6</sup>, -COR<sup>6</sup>, -CONR<sup>6</sup>R<sup>7</sup> and -(CH<sub>2</sub>)<sub>m</sub>OC(O)C<sub>1-4</sub>alkyl;

R<sup>5</sup> represents a hydrogen atom or a C<sub>1-6</sub>alkyl group optionally substituted by one or two substituents selected from C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, hydroxy or -NR<sup>6</sup>R<sup>7</sup>;

5 R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> which may be the same or different, each independently represent a hydrogen atom or a C<sub>1-6</sub>alkyl group; or -NR<sup>6</sup>R<sup>7</sup> forms a saturated heterocyclic ring which has 5 or 6 ring members which, when there are 6 ring members, may optionally contain in the ring one oxygen or sulphur atom;

10 R<sup>9</sup> represents a hydrogen atom or a C<sub>1-6</sub>alkyl, -COR<sup>10</sup> or -SO<sub>2</sub>R<sup>11</sup> group; or -NR<sup>8</sup>R<sup>9</sup> forms a saturated heterocyclic ring which has 5 or 6 ring members, may optionally be substituted by an oxo group and, when there are 6 ring members, may optionally contain in the ring one oxygen or sulphur atom;

15 R<sup>10</sup> represents a hydrogen atom or a group selected from C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy or a C<sub>1-4</sub>alkoxyalkyl group;

R<sup>11</sup> represents a C<sub>1-6</sub>alkyl or phenyl group;

X represents -CONH-, -NHCO-, -CH<sub>2</sub>NH- or -NHCH<sub>2</sub>-;

m represents an integer from 1 to 3;

n represents zero or an integer from 1 to 3;

p represents an integer from 1 to 3; and

20 q represents an integer from 1 to 3.

2. Compounds as claimed in Claim 1 for use in therapy.

Patents Act 1977  
 Examiner's report to the Comptroller under Section 17  
 (The Search report)

- 1 -

Application number  
 GB 9305469.0

<b>relevant Technical Fields</b>  (i) UK Cl (Ed.M) C2C (ii) Int Cl (Ed.5) C07D	<b>Search Examiner</b> <b>R HONEYWOOD</b>
	<b>Date of completion of Search</b> <b>13 MAY 1994</b>
<b>Databases (see below)</b> (i) UK Patent Office collections of GB, EP, WO and US patent specifications.  (ii) ONLINE DATABASE - CAS ONLINE	<b>Documents considered relevant following a search in respect of Claims :-</b> 1-2

**Categories of documents**

- X:** Document indicating lack of novelty or of inventive step.  
**Y:** Document indicating lack of inventive step if combined with one or more other documents of the same category.  
**A:** Document indicating technological background and/or state of the art.
- P:** Document published on or after the declared priority date but before the filing date of the present application.  
**E:** Patent document published on or after, but with priority date earlier than, the filing date of the present application.  
**&:** Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
	NONE	

**Databases:** The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).